Mixed Effects, Growth Curves, and Longitudinal Models

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Objectives

- To understand
  - the difference between fixed and random effects
  - the benefits and limitations of growth curve models
  - the need to adjust for within-person correlation

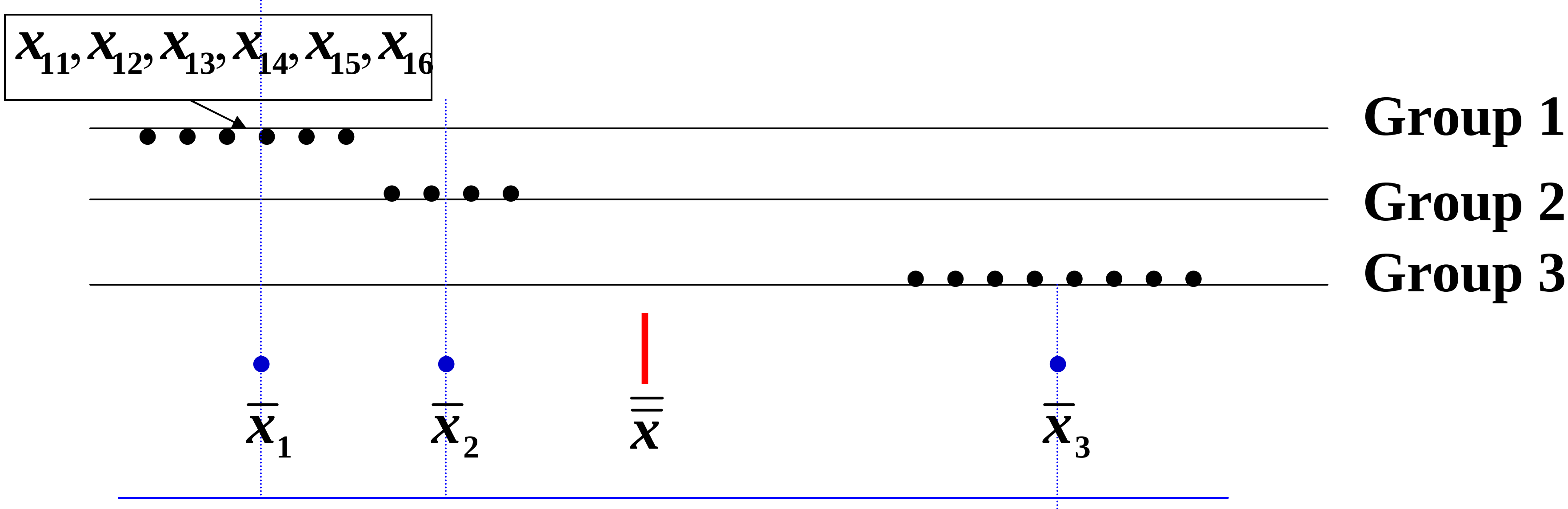
Warning

- This is a very difficult subject to tackle with no formulas
- Promise: I will keep them to a minimum

Review of Analysis of Variance

- Extension of two-sample t-test to more than 2 groups
- Compare variability within a group (error) to the variability between groups

Large Group Separation

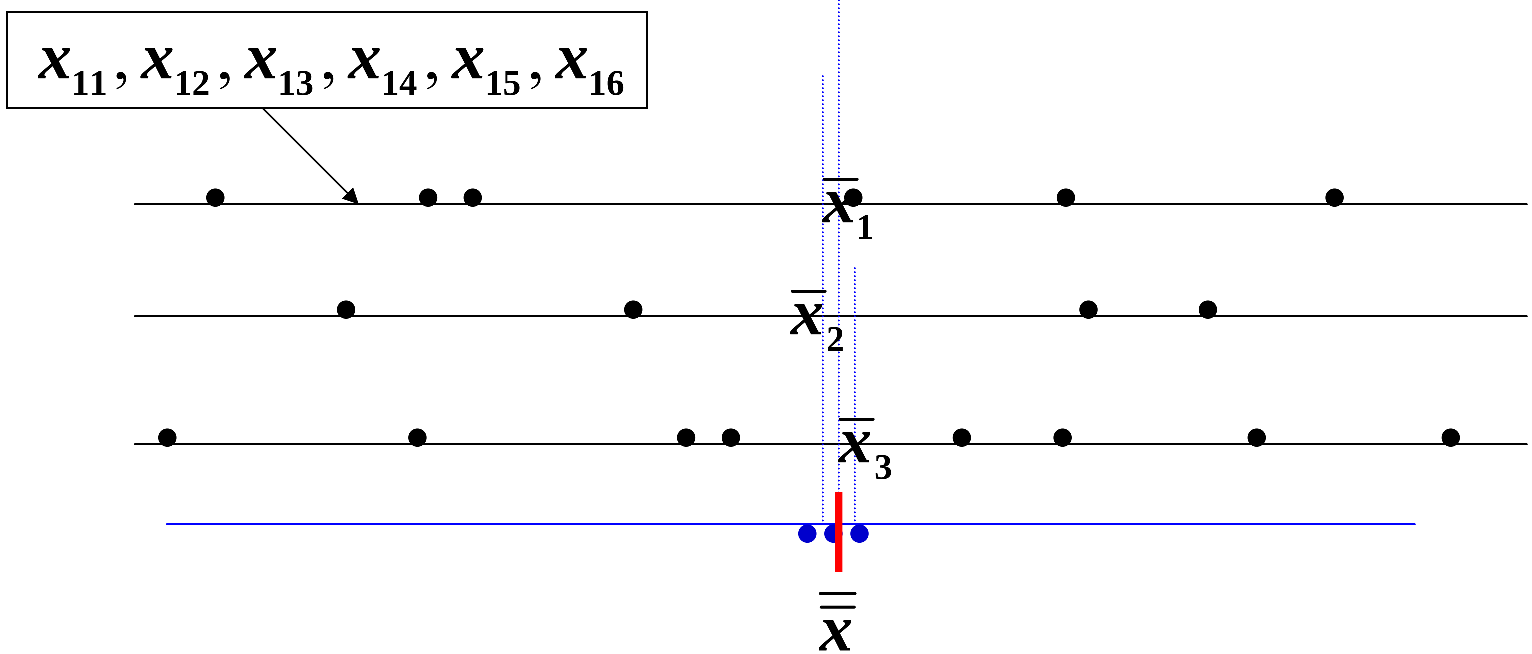


$$\bar{\bar{x}} = \frac{n_1 \bar{x}_1 + n_2 \bar{x}_2 + \cdots + n_k \bar{x}_k}{n}$$

$x_{ij} - \bar{x}_i$ **= within group variability**

$\bar{x}_i - \bar{\bar{x}}$ **= between group variability**

Small Group Separation



$$x_{ij} - \bar{x}_i \quad \text{= within group variability}$$

$$\bar{x}_i - \bar{\bar{x}} \quad \text{= between group variability}$$

One-Way Analysis of Variance

- **Hypotheses:** $\boldsymbol{H_0}$: $\boldsymbol{\mu_1 = \mu_2 = \cdots = \mu_k}$

  $\boldsymbol{H_1}$: $\boldsymbol{\mu_i \neq \mu_j}$ **for some** $\boldsymbol{i, j = 1, \cdots, k}$

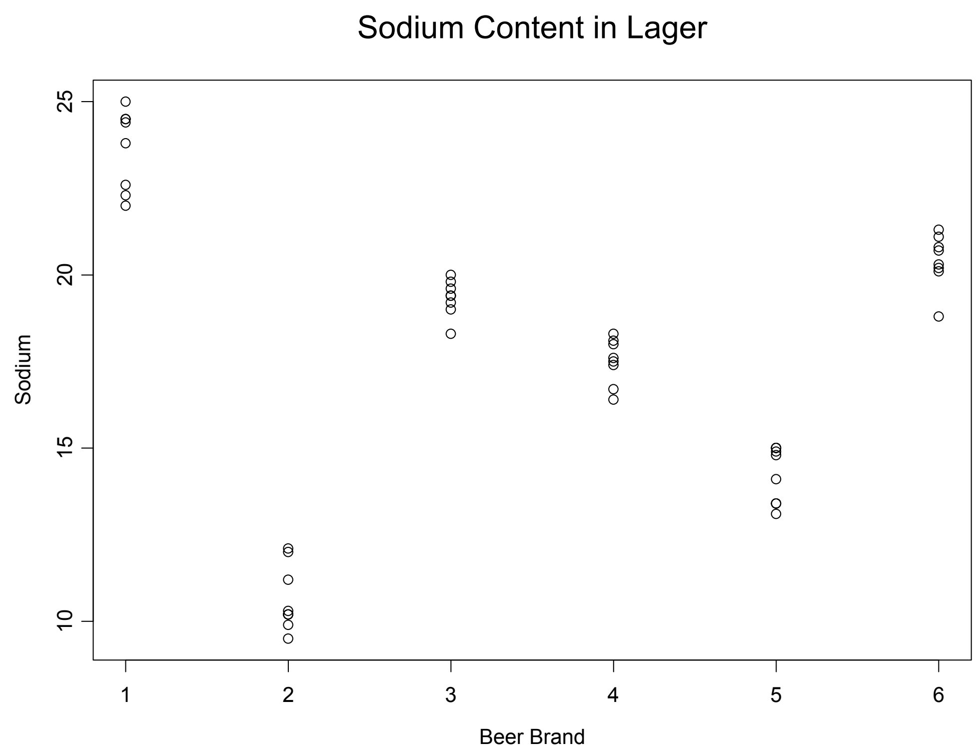
- **Test statistic:**

$$F = \frac{\text{Variation among the sample means}}{\text{Variation among individuals w/in groups}} = \frac{\overbrace{\dfrac{\sum_{i=1}^{k}\sum_{j=1}^{n_i}(\bar{x}_i - \bar{\bar{x}})^2}{(k-1)}}^{\text{MSB}}}{\underbrace{\dfrac{\sum_{i=1}^{k}\sum_{j=1}^{n_i}(x_{ij} - \bar{x}_i)^2}{(n-k)}}_{\text{MSW}}}$$

$$\sim \boldsymbol{F_{k-1, n-k}}$$

Simple Example

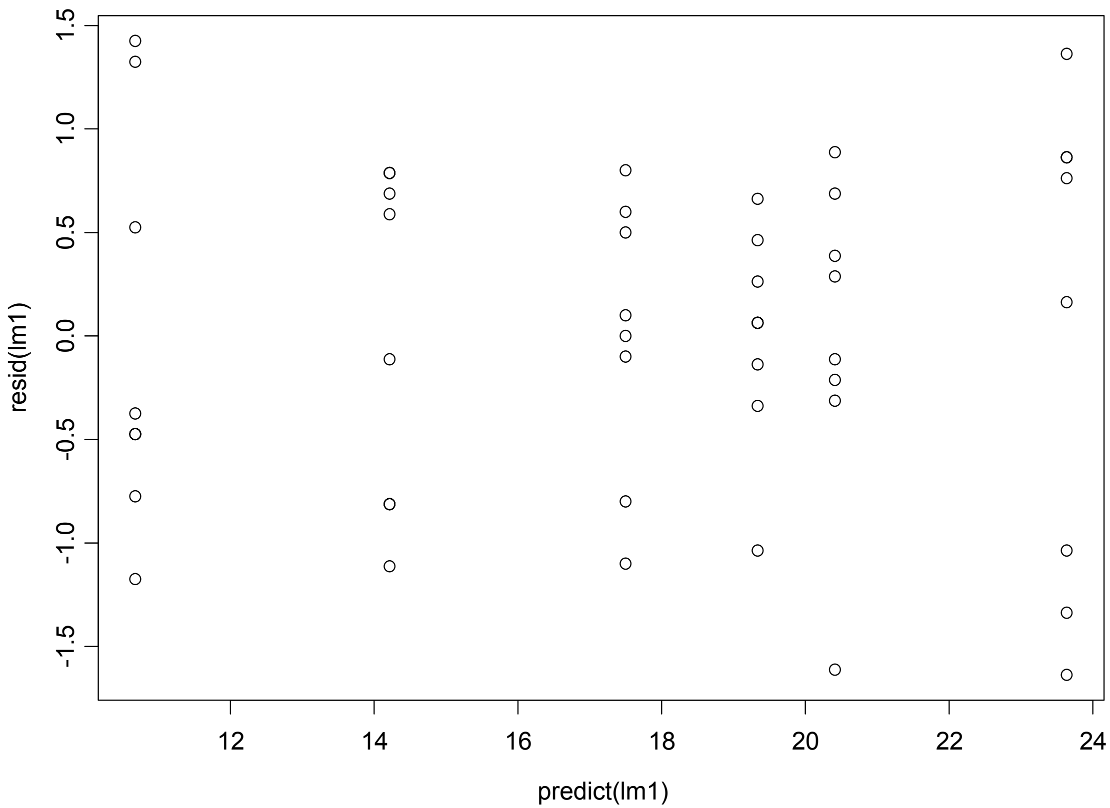
- Measure sodium content in eight samples of each of six brands of beer



ANOVA Analysis

- Question: Do the mean levels of sodium in beer differ between these six brands?
- $Y_{ij}=\mu_i=\alpha+\beta_i+\varepsilon_{ij}$ where i=brand, j=sample
- ε_{ij} is the error, normally distributed with variance σ^2 and mean 0
- The null hypothesis is that $\beta_1=\beta_2= \ldots=\beta_5=\beta_6$
- That is, all β_i's are equal which would mean that the mean levels of Y_{ij} are the same for all brands
- P-value<0.0001 using an F-test
- Interpretation: Sodium content varies across these six brands of beer

Residual Plot



Random Effects Analysis

- Question: Does sodium content vary across brands of beer?
- $Y_{ij}=\alpha+\beta_i+\varepsilon_{ij}$ where brand, j=sample
- ε_{ij} is the error, normally distributed with variance σ^2 and mean 0
- We're not interested in these six particular brands of beer, but in whether there is beer to beer variability
- β_i is a random effect, norm dist with variance σ_β^2 and mean 0
- The null hypothesis is that σ_β^2 =0, no variability between β_i's
- If σ_β^2=0, then all β_i=0
- P-value<0.0001 *using the same F-test*
- Interpretation: Sodium content varies across beer brands

Model consequences

- The variance of Y is the sum of within and between variances
- $Var(Y_{ij}) = Var(\alpha+\beta_i+\varepsilon_{ij}) = \sigma^2 + \sigma_\beta^2$
- Two samples of beer from the same brand are more similar than samples of two different brands
  - Two samples of the same brand: Correlation is $\sigma_\beta^2/(\sigma^2 + \sigma_\beta^2)$
  - Different brands of beer: Correlation is 0

Definitions

- “A factor is random if its levels consist of a random sample of levels from a population of possible levels”
- “A factor is fixed if its levels are selected by a nonrandom process or if its levels consist of the entire population of possible levels”
- Milliken and Johnson

Random or Fixed?

- "If some form of randomization is used to select the levels included in the experiment, then the factor is random." Milliken and Johnson
- Be careful—clinics may or may not have been selected at random

Fixed and Random Effects

- Fixed Effects
  - Subject information
  - Usually care about these effects (e.g., gender)
  - Often of primary interest
- Random effects
  - Adjusts for correlation within subject, family, practice, etc.
  - Usually don't care about these effects (e.g., subject, clinic)
  - Often nuisance parameters

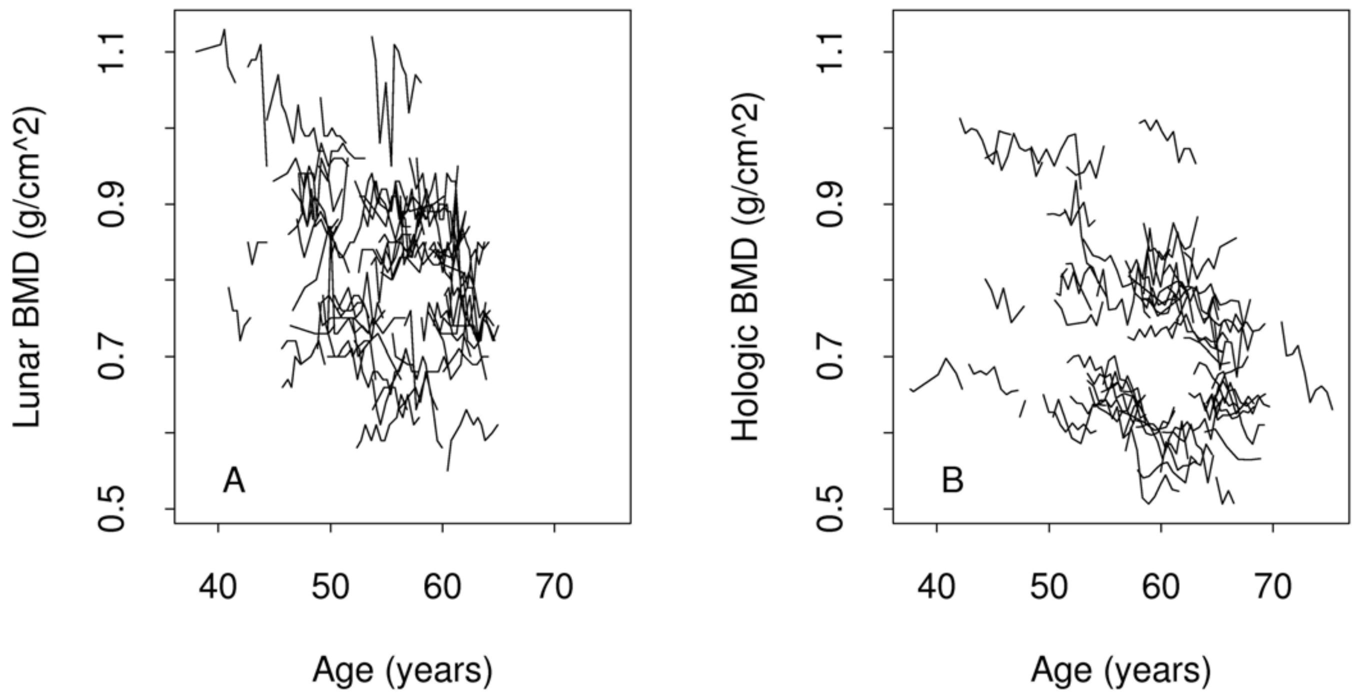
Mixed models

- Contain both fixed and random effects
- Usually fit using “maximum likelihood”
- That is, pick model parameters that would maximize the chance of observing the data that was actually observed

Growth Curve Models

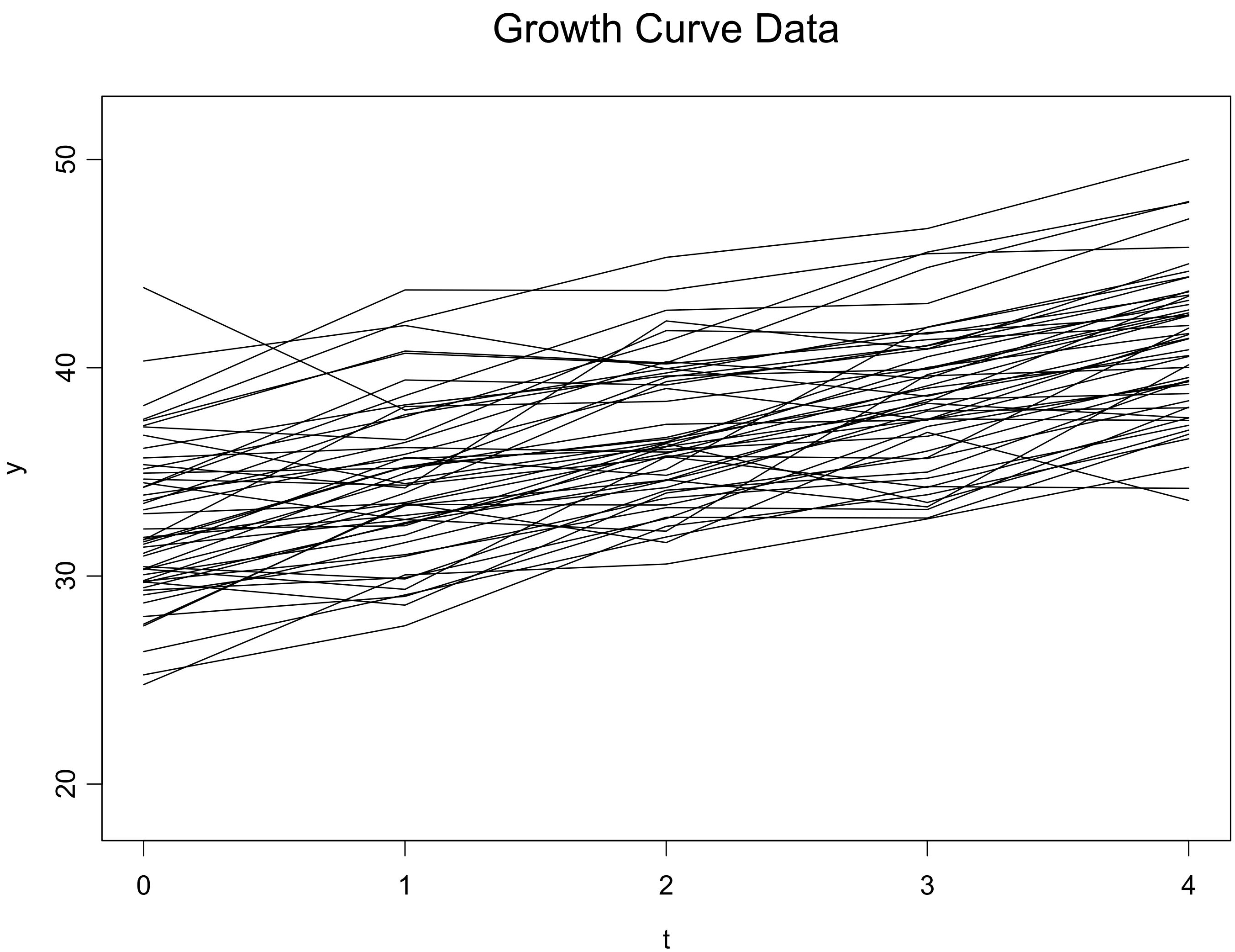
- Also called "Latent Growth Curve Modeling"
- Similar to Analysis of Covariance (ANCOVA)
- Data within a person are assumed to change linearly over time
- Each person has a subject-specific intercept and slope
- Might be over used in RCTs

Example—Bone Mineral Density



Ambrosius and Hui, Statistics in Medicine, 2004

Simulated Growth Curve Example



Growth Curve Model

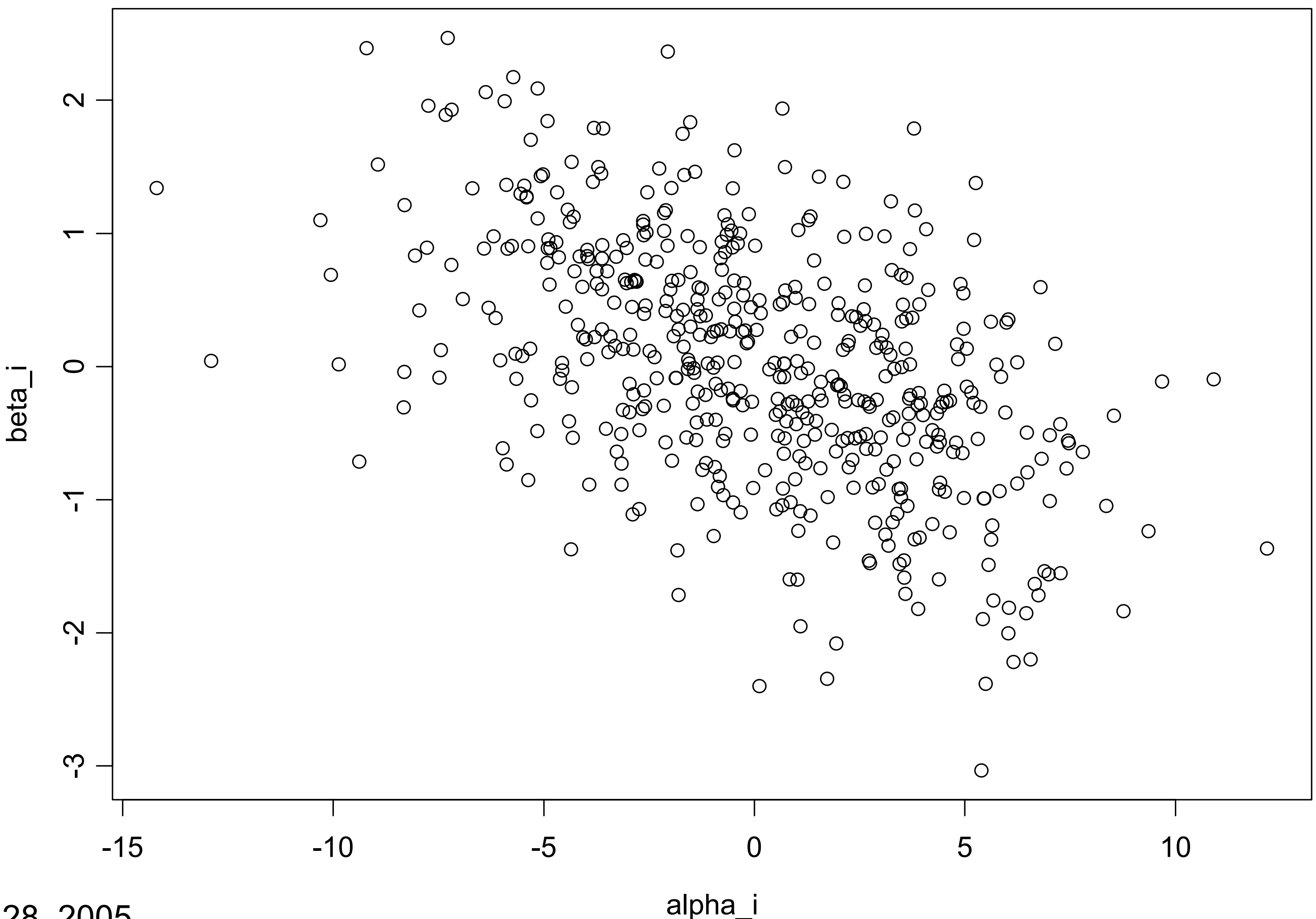
- $Y_{ij}=(\alpha + \alpha_i)+ (\beta + \beta_i)\, t_{ij} + \varepsilon_{ij}$
- i denotes subject and j denotes time
- Have both fixed (α and β) and random components (α_i, β_i, and ε_{ij})
- α_i and β_i are jointly correlated and independent of ε_{ij}
- α_i and β_i are latent variables-LGC

$$\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_\alpha^2 & \sigma_{\alpha\beta} \\ \sigma_{\alpha\beta} & \sigma_\beta^2 \end{pmatrix} \right) \qquad \varepsilon_{ij} \sim N\left(0, \sigma^2\right)$$

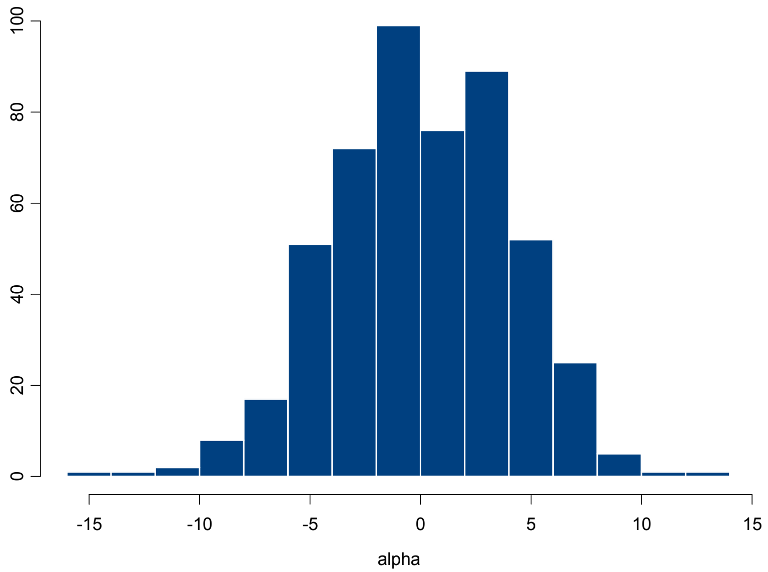
Model Implications

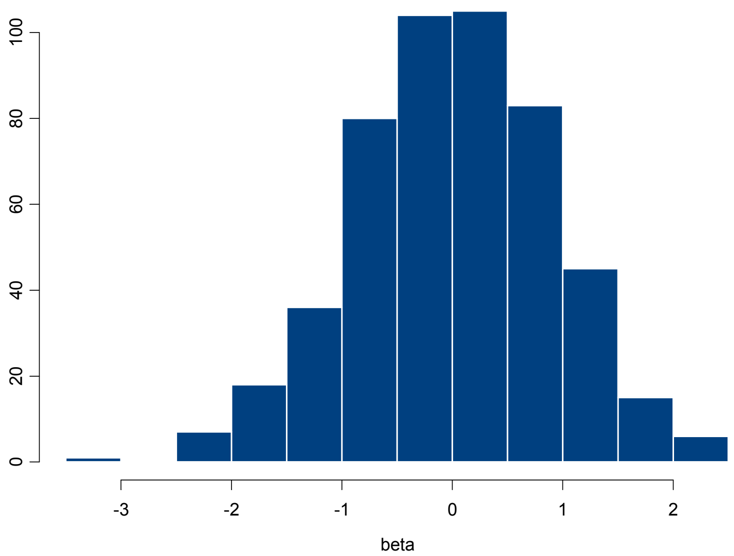
- Data within a subject are correlated
  - $\mathrm{Cov}(Y_{ij}, Y_{ij'})$ = ...BMOA…= $\sigma_\alpha^2 + (t_{ij}+t_{ij'})\,\sigma_{\alpha\beta} + t_{ij}\, t_{ij'}\, \sigma_\beta^2$
  - $\mathrm{Var}(Y_{ij}) = \sigma_\alpha^2 + 2\, t_{ij}\, \sigma_{\alpha\beta} + (t_{ij'})^2\, \sigma_\beta^2$
- Work with someone familiar with these models when you first use them!

Bivariate Normality

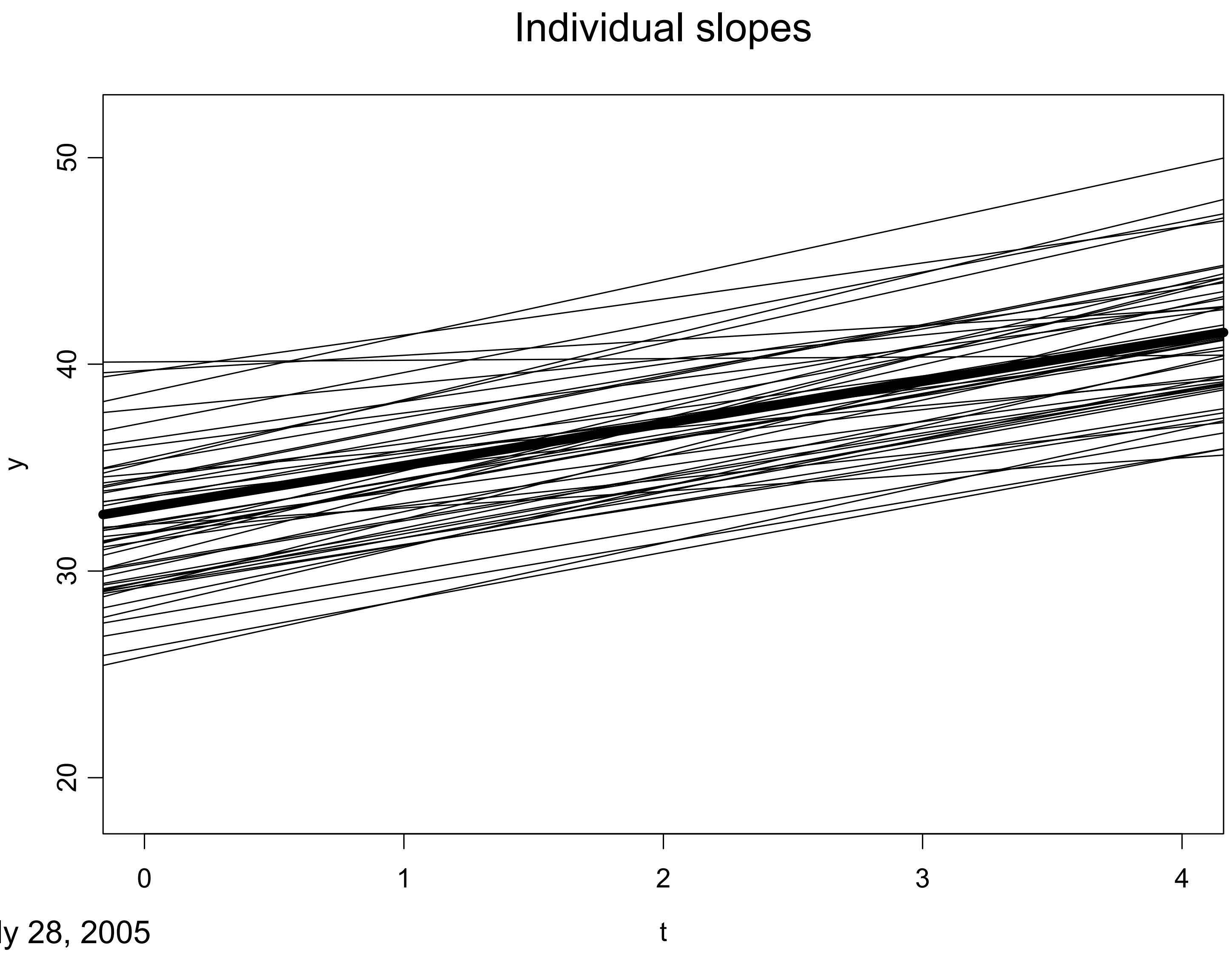


Marginal distributions are normal





Fitted Growth Curve Model



Fitted Model

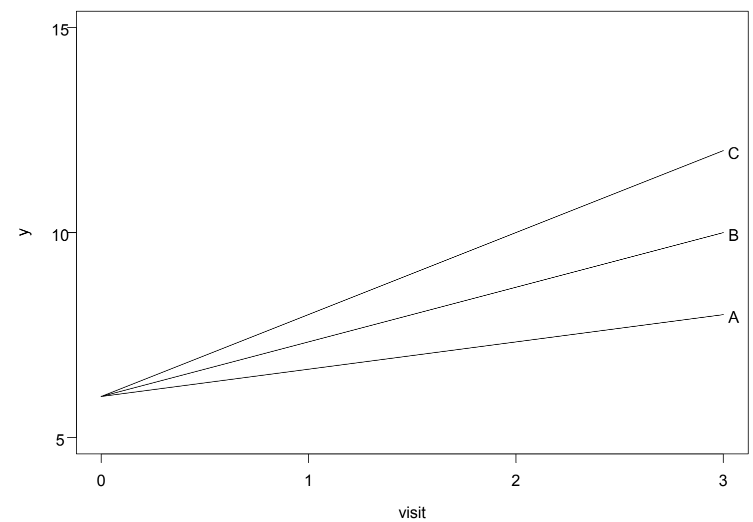
- $Y_{ij} = \alpha + \alpha_i + (\beta + \beta_i)\, t_{ij} + \varepsilon_{ij}$
- $Y_{ij} = 33.06 + 2.04\, t_{ij}$

$$\begin{pmatrix} \alpha_i \\ \beta_i \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 16.41 & -1.94 \\ -1.94 & 0.86 \end{pmatrix} \right)$$

$$\varepsilon_{ij} \sim N(0, 2.23)$$

Use in RCTs

- Does rate of change differ between treatment and control?
- Does intercept differ? Usually groups are “the same” at baseline in RCTs although there will be slight differences

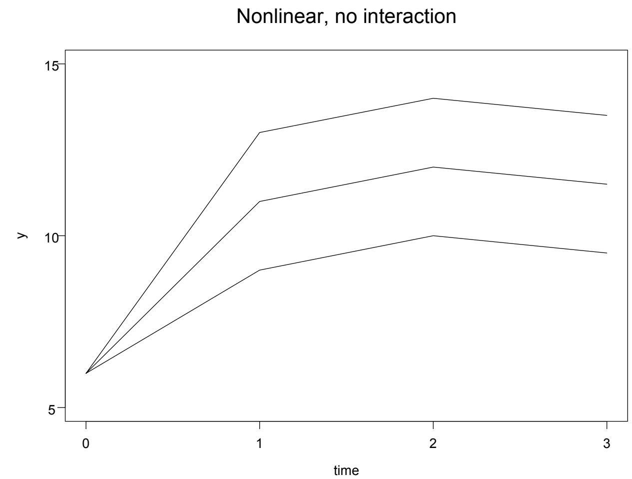


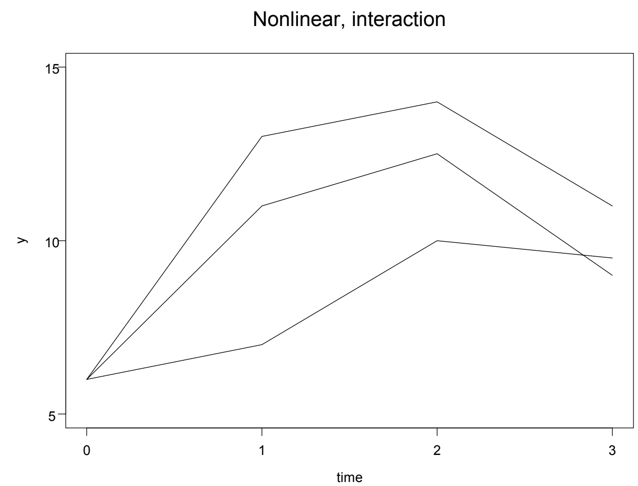
Different Lines

- Extension of previous model
- $Y_{ijk}=(\alpha + \alpha_i + \gamma_k) + (\beta + \beta_i + \delta_k)\, t_{ijk} + \varepsilon_{ijk}$
- k indicates group
- γ_k is effect of treatment on intercept—should be close to 0 in RCT
- δ_k is effect of treatment on slope—usually of primary interest in these models
- May also have other covariates

Growth Curves Considerations

- Seems to be in vogue but is not a panacea
- Assumes linearity of treatment over time
- Often see an early effect followed by maintenance
- Uses fewer degrees of freedom for time than using time as a factor
- Growth curve models are a special case of mixed models, much like regression is a special case of ANOVA
- Careful: I’ve seen really bad grant applications using latent growth curves. (E.g., assuming slope of placebo group is 0)





Longitudinal Mixed Models

- Other kinds of mixed models that don't assume linearity
- Mixed models can account for within person correlation (as well as within family, within practice, etc.)

Why Adjust for Correlation?

- Subjects within clusters are usually correlated (families, practices, sites, etc.)
- Measurements on the same subject are usually correlated
- Ignoring correlations usually results in a belief that we have more information than we do
- Ignoring correlations increases chance of falsely rejecting the null

Adjusting for Correlation

- Compound Symmetry

$$\sigma^2 \begin{bmatrix} 1 & \rho & \rho \\ \rho & 1 & \rho \\ \rho & \rho & 1 \end{bmatrix}$$

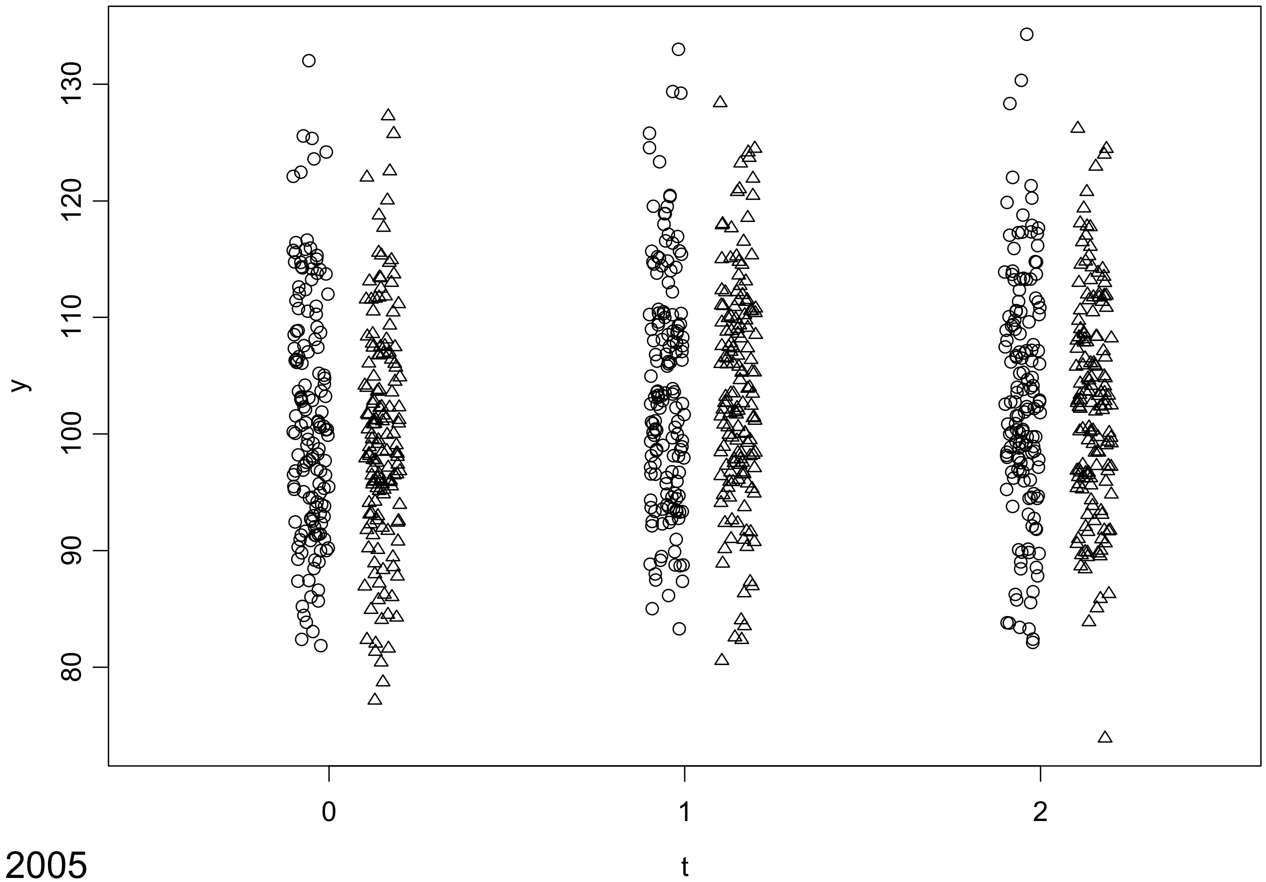
- CS used in repeated measures analysis of variance

- Unstructured

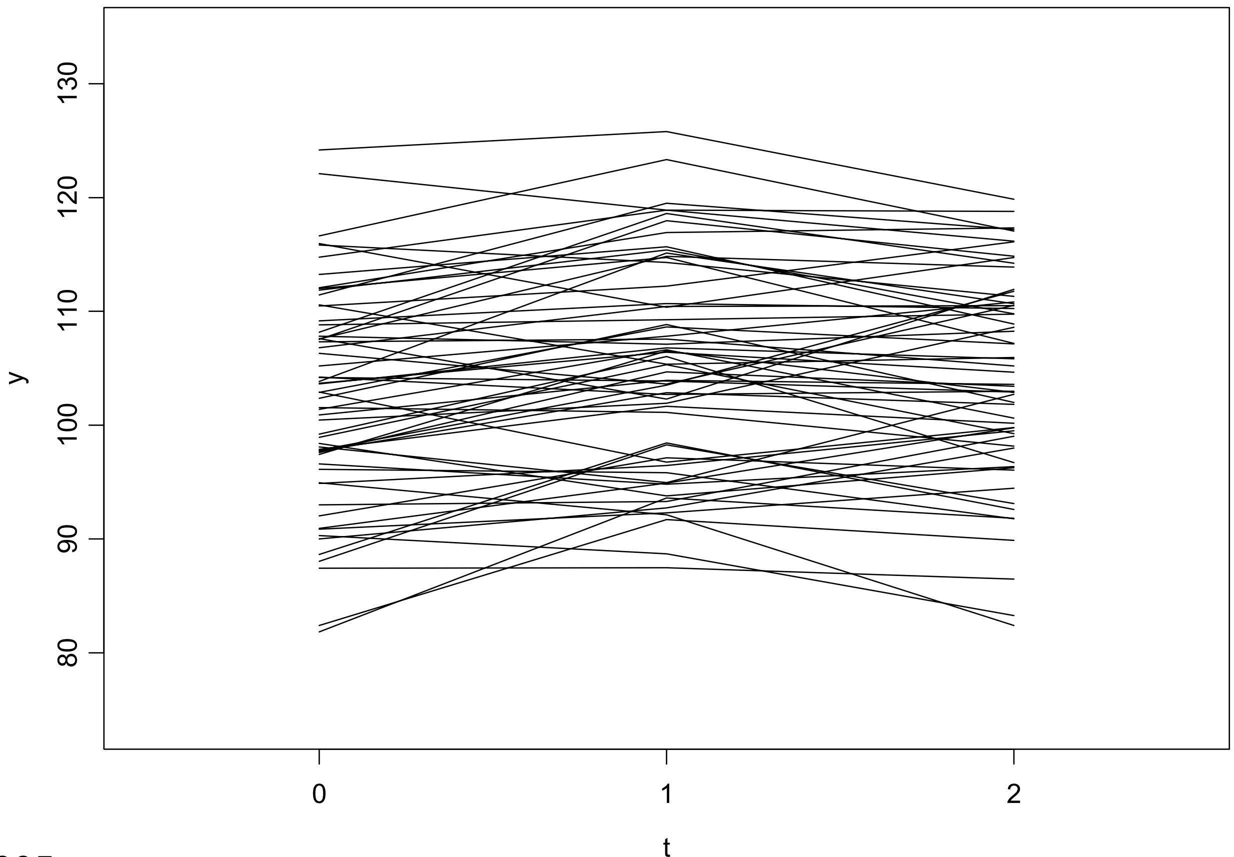
$$\begin{bmatrix} \sigma_1^2 & \rho_{12} & \rho_{13} \\ \rho_{12} & \sigma_2^2 & \rho_{23} \\ \rho_{13} & \rho_{23} & \sigma_3^2 \end{bmatrix}$$

- And many more…(SAS manual lists 31)

Longitudinal Mixed Model Example



Within-Subject Correlation



Example

- Sample Means:
  - Treatment: 100.1, 103.8, 102.7
  - Control: 101.4, 103.7, 103.1
- Simulated with means of
  - Treatment: 100, 103, 102.5
  - Control: 100, 102, 101.5
- Simulated with ρ=0.9 so there is a lot of within-subject correlation

$$100\begin{bmatrix} 1 & 0.9 & 0.9 \\ 0.9 & 1 & 0.9 \\ 0.9 & 0.9 & 1 \end{bmatrix}$$

Methods of Analysis

Method	Outcome	Adjust for Baseline	Account for Correlation	P-Value
T-test	FU2	No	-	0.7503
ANOVA	FU2	Yes	-	0.1461
ANOVA	FU1 & FU2	Yes	No	0.0060*
Mixed	FU1 & FU2	No	Yes	0.8838
Mixed	FU1 & FU2	Yes	Yes	0.0229

* Don’t use!!!

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  - the difference between fixed and random effects
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References

- Ambrosius WT, Hui SL. *Cross Calibration in Longitudinal Studies*, Statistics in Medicine, 2004, 23:2845-2861
- Milliken GA, Johnson DE, Analysis of Messy Data, Volume I: Designed Experiments, Chapman & Hall, London, 1992
- Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS System for Mixed Models, SAS Institute, Cary, NC, 1996

Bonus: Effect of Adjusting For Strata

- 2 groups, 2 strata
- p=proportion in stratum 1
- s=stratum difference
- Y=outcome
- $\mathrm{Var}[Y|\text{group and stratum}]=\sigma^2$
- $\mathrm{Var}[Y|\text{group}]=s^2p(1-p)+\sigma^2$
- The latter is larger and results in lower power